REMARKS

I. The Invention

The present invention describes a recombinant vector useful for inducing a tumor-specific immune response against B-cell lymphoma, by way of a fusion protein of a cytokine and a tumor-specific idiotype. Rather than directly encoding the fusion protein, which would require individual cloning of the idiotype of every patient's lymphoma cells, the expression vector of this invention includes a sequence of at least 1.5 kb that is homologous to an at least 1.5 kb segment of the μ intron or the k intron, such that, following transfection of a B lymphoma cell and subsequent homologous recombination, the DNA sequences coding a cytokine and a immunoglobulin constant region (or a part thereof) also present in the vector are incorporated into the malignant B cell's genomic sequence. A cytokine fusion protein is then produced by the B cell to include the specific idiotype encoded by the endogenous sequence of the malignant B cell. After rendered incapable of proliferation, such a malignant B cell expressing a tumor immunoglobulin-cytokine fusion protein can be reintroduced into a patient to elicit a specific anti-B cell lymphoma immunity due to enhanced recruitment of antigen-presenting cells by the cytokine and more effective presentation of the tumor-specific immunoglobulin idiotype. This invention eliminates the need to clone each patient's idiotypic domain and is thus quick, convenient, and less expensive.

II. Status of the Claims

Claims 1-5, 7-9, 11-17, and 29 are pending and stand rejected. Upon entry of the present amendment, claims 1-3 recite a "continuous region of at least 1.5 kb," which finds support throughout the entire specification. For example, in the last paragraph on page 9, it is stated that the vector of this invention has "***a*** region of at least 1.5 kb with homology to an intron region"; in the last paragraph on page 10, it is stated that, "[t]he homologous sequence contained in said vector must have a length of at least 1.5 kb to achieve a homologous recombination event at all." These statements make it clear that it is one single region, *i.e.*, a continuous, undisrupted

region, of a length of at least 1.5 kb that is necessary to ensure the recombination event.[1] Furthermore, the concept of a continuous region of at least 1.5 kb is also presented in German patent document DE 44 06 512, which is incorporated by reference in this application (see the second full paragraph on page 9). The present application indicates that the starting material for the construction of the vectors of this invention was the integration vectors described in DE 44 06 512. See page 8, the first full paragraph, of the present application. DE 44 06 512 in turn describes in Example 1 that the overall homology flank had a length of 3.0 kb and then a 1.0 kb fragment was excised. In other words, the remaining homologous region was a 2.0 kb continuous sequence. As such, this application provides inherent support for the claim language "a continuous region of at least 1.5 kb."

This claim amendment was not made earlier because Applicant in good faith believed that all necessary amendment for overcoming the outstanding rejections had been made. Because the present claim amendment adds no new matter and requires no new search, entry of the amendment is respectfully requested.

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[1] In the last paragraph on page 7 of the Final Office Action mailed January 6, 2009, the Examiner asserts,

> Applicant's argument that unless the region is continuously at least 1.5 kb in length or it will not work is not supported by any evidence. Applicant is specifically directed to the teaching of Polack et al., as evidenced by Mucke et al., who teach that such a segment does in fact work. (emphasis in original)

In response, Applicant first notes that the Examiner's statement amounts to an acknowledgment that Polack/Mucke does not teach a region that is continuously at least 1.5 kb. Secondly, Applicant respectfully reminds the Examiner that the vector of the present invention is fundamentally different from Polack's vector: the vector of this invention is an integration vector, which carries a cytokine coding sequence but does not directly express the cytokine; instead, the μ or k intron homologous sequence within the vector directs a recombination event, causing the cytokine coding sequence to be integrated into a host tumor cell's genome and joined with a genomic sequence encoding a tumor-specific idiotype. The fusion protein of cytokine and tumor-specific idiotype is then expressed from the "new" genomic sequence resulted from the recombination. In contrast, Polack's vector is a conventional expression vector containing a promoter and a protein coding sequence, so that the protein is directly expressed from the vector. Polack's vector does not cause any targeted genomic recombination/integration, and does not become a part of the genomic sequence. As such, even if Polack's vector does work for its intended purpose (*i.e.*, direct expression of a coding sequence entirely present in the vector), the less than 1.5 kb segment cannot be said as "does in fact work" for the purpose of homologous recombination and genomic integration, which is essential for the vector of this invention to express the cytokine-tumor-specific idiotype fusion protein.

III. Claim Rejections

A. 35 U.S.C. §112, First Paragraph: Written Description

Claims 1-5, 7-9, and 11-17 remain rejected under 35 U.S.C. §112, first paragraph, for alleged inadequate written description. Applicant again traverses the rejection for the same reasons already made of record in Applicant's earlier responses.

The pending claims are drawn to a recombination vector for expressing immunoglobulin-cytokine fusion proteins in malignant B cells. The vector comprises the following components operably linked to each other: (a) a continuous region of at least 1.5 kb that is homologous to an at least 1.5 kb segment of the μ intron or the k intron; (b) at least one DNA sequence encoding a constant region of an immunoglobulin or a part of the constant region; (c) a DNA sequence encoding a cytokine; and (d) a marker gene that is selectable in eukaryotic B cells and contains a functional enhancer region.

To reiterate Applicant's position, at the effective filing date of this application, all of these common components of the claimed vector--μ or k intron sequences, immunoglobulin constant region sequences, cytokine sequences, selectable marker sequences, and enhancer sequences, were well known and available to a person of ordinary skill in the art. An artisan upon reading the present disclosure would therefore reasonably conclude that the present inventor had in his possession these components and therefore the claimed vector. As such, the present disclosure meets the written description requirement under 35 U.S.C. §112, first paragraph, which requires a patent specification to describe the claimed invention in sufficient detail such that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention at the time of filing.

On page 2 of the Final Office Action mailed January 6, 2009, the Examiner once again relies on *University of Rochester v. G.D. Searles & Co.*, 69 USPQ2d 1886 (Fed. Cir. 2004) and *Ex parte Kubin*, 83 USPQ2d 1410 (Bd. Pat. App. & Int. 2007), and argues that the written description requirement is not met merely by demonstrating one's ability to possess the claimed invention. The Examiner stresses the distinction between the ability to obtain the invention and

the inventor's being in possession of the invention. Applicant understands this distinction and, based on this understanding, again contends that the instant disclosure, especially in light of the state of the art, clearly shows both a skilled artisan's ability to obtain the invention and inventor's being in possession of the invention. Unlike in *Rochester* or *Kubin*, the genera of μ or k intron sequences, immunoglobulin constant region sequences, cytokine sequences, selectable marker sequences, or enhancer sequences were well known in the art. The Examiner's analysis of "representative number of species" or "common structural features" and conclusion pertain to a patent applicant's attempt to broadly claim a genus of previously unknown species and thus have no relevance in the present case.

In short, the written description rejection stands for the proposition that an artisan of ordinary skill would not be convinced of Applicant's possession of the claimed vector, even though the components of the vectors, μ or k intron sequences, immunoglobulin constant region sequences, cytokine sequences, selectable marker sequences, and enhancer sequences, were all known in the art at that time. This is not a tenable position. Furthermore, the large number of possible selections within each genus of ***known*** components is evidence of a broad scope of enablement and possession of the invention, not remotely akin to the "hunting" for the unknown referred to by the Supreme Court in *Brenner*. Contrary to the Examiner's position, one's ability to choose from a broad range of ***known*** components to practice a claimed invention in fact supports the conclusion of inventor's having possession of the invention.

For these reasons as well as those already made of record in Applicant's previous responses, it is respectfully submitted that the instant application has fully met the written description requirement under 35 U.S.C. §112, first paragraph. It is therefore respectfully requested that the Examiner withdraw the written description rejection.

B. 35 U.S.C. §102

Claims 1-5, 7-9, 11, 13-17, and 29 are rejected for alleged anticipation under 35 U.S.C. §102(e) by Polack *et al.* (U.S. Patent No. 6,521,449) as evidenced by Mucke *et al.* (*Gene*

Therapy **4**:82-92, Feb. 1997). Applicant respectfully traverses the rejection, particularly in view of the present claim amendment.

Applicant contends that not neither Polack nor Mucke provides all limitations of the pending claims. For instance, the limitation of "a continuous region of at least 1.5 kb which is homologous to an at least 1.5 kb segment of the μ intron or the *k* intron" can be found in neither of the two references. As the Examiner has acknowledged, Polack describes the combined use of two enhancer κ intron elements, which provide a combined length of over 1.5 kb but each is less than 1.5 kb. Because neither Polack nor Mucke provides the limitation of "a continuous region of at least 1.5 kb which is homologous to an at least 1.5 kb segment of the μ intron or the *k* intron," there is no basis to support the anticipation rejection. Withdrawal of the rejection under 35 U.S.C. §102(e) is therefore respectfully requested.

C. 35 U.S.C. §103

Claims 1-5, 7-9, 11-13, and 15-17 are rejected under 35 U.S.C. §103 for alleged obviousness over Polack in view of Levy and Gillies. Claims 1-5, 7-9, and 11-17 are further rejected under 35 U.S.C. §103 for alleged obviousness over Polack or Mucke in view of Mocikat (*Immunology* **84**:159-163, 1995). Applicant respectfully traverses the rejections.

In order to establish a *prima facie* showing of obviousness, three requirements must be satisfied: all limitations of a pending claim must be expressly or impliedly disclosed by prior art references; there must be a suggestion or motivation in the art for one skilled artisan to combine the limitations; and there must be a reasonable expectation of success in making such a combination. MPEP §2143. As discussed above, neither of the primary references by Polack *et al.* and Mucke *et al.* provide all limitations of the pending claims. On the other hand, the secondary references, Levy, Gillies, and Mocikat, are cited to provide teaching of a vector encoding an idiotype/GM-CSF fusion protein, a vector encoding a recombinant antibody-cytokine fusion protein, and a vector for homologous recombination at the Ig locus, respectively. None of the Levy and Gillies references provide at least one missing element, namely the region of a continuous sequence at least 1.5 kb in length which is homologous to an at least 1.5 kb

segment of the μ intron or the k intron as recited in (a) of claim 1. Without providing all claim limitations, Polack, Levy, and Gillies together cannot support a *prima facie* case of obviousness.

The Examiner takes the position that, since Mocikat *et al.* included a 2.3 kb fragment of the mouse μ intron sequence in their recombination vector, the missing claim limitation is supplemented. The Examiner further contends that Mocikat provides a motivation to combine its teaching with that of Polack, because Mocikat allegedly teaches various advantageous features of this 2.3 kb mouse μ intron fragment (see the last paragraph on page 10 and also the paragraph bridging pages 11 and 12 of the Final Office Action). Applicant disagrees with the Examiner's arguments for at least two reasons: first, because of the fundamental differences in purpose and mechanism of action between expression vectors (*e.g.*, the Polack vector) and integration vectors (*e.g.*, the Mocikat vector), discussed in the footnote on page 6 of this paper, there would be no motivation for a skilled artisan to combine the teaching of the Polack and Mocikat references. The advantages in protein expression that the Examiner has alleged Mocikat's 2.3 kb mouse μ intron sequence would confer relate solely to the expression of rearranged genomic sequence resulted from homologous recombination and genomic integration, crucial for an integration vector to effectuate gene expression as intended. The recombination/integration process, however, is completely irrelevant to the direct expression of a recombinant protein, which is how an expression vector such as the Polack vector works. Therefore, the advantages of the 2.3 kb mouse μ intron fragment present in Mocikat's integration vector will not provide any motivation for a skilled artisan to use the fragment in Polack's expression vector.

Second, if anything is suggested by Polack, Mucke, and Mocikat together, it is to teach away from any consideration of replacing the enhancers used by Polack with the 2.3 kb μ intron sequence used by Mocikat to modify Polack's expression vector. This is because the Polack vector is an expression vector and uses enhancers to promote the expression of a coding sequence carried by the vector. Replacing the enhancers with the 2.3 kb intron sequence would completely defeat this purpose. As such, there is at least one obvious reason to NOT combine

Polack, Mucke, and Mocikat. With this "teaching away" in the cited references, Applicant contends that no *prima facie* obviousness is or can be established.

Accordingly, Applicant respectfully requests withdrawal of the rejections under 35 U.S.C. §103(a).

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

/Chuan Gao/

Chuan Gao
Reg. No. 54,111

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
C2G:c2g
61940713 v1